provides high level production of the antigens in substantially pure form. The purified antigens are useful for detecting type-specific herpes simplex virus infections.

In the Advisory Action mailed April 24, 1997, the Examiner indicated that the proposed amendment mailed March 14, 1997 would be entered only upon filing a Notice of Appeal. Because a Notice of Appeal has not been filed, applicants assume that the proposed amendment mailed March 14, 1997 was not entered and respectfully request entry of the amendment set forth above.

Objection to the Claims

In the Office Action mailed November 14, 1996, the Examiner objected to Claim 16 on the basis that the claim contained a typographical error. Applicants have amended line 2 of Claim 16 to replace "hespes" with the word "herpes".

Rejections Under 35 U.S.C. §§102(b) and 103

In the Office Action mailed November 14, 1996, the Examiner rejected Claims 7, 8, and 16 under 35 U.S.C. §102(b) as anticipated by or under 35 U.S.C. §103 as obvious over the article by Lee, Francis K., *et al.*, "Detection of Herpes Simplex Virus Type 2-Specific Antibody with Glycoprotein G," *J. Clin. Microbiol.* 22(4):641-644 (October 1985) or the article by Lee, Francis K., *et al.*, "A Novel Glycoprotein for Detection of Herpes Simplex Virus type 1-specific Antibodies," *J. Virol. Methods* 14:111-118 (1986). The Examiner noted that the cited articles teach the production and use of herpes simplex virus gG-1 and gG-2 antigens, the rejected claims are product-by-process claims, and patentable distinctions between the material, structural, and functional characteristics of the claimed compositions and the prior art compositions had not yet been demonstrated. Applicants respectfully submit that the amendments to the claims overcome the rejection.

Claims 7 and 8 have been amended to clarify that the claimed herpes simplex virus gG-1 and gG-2 antigens are **recombinant** antigens. Claim 16 also specifies that the claimed antigens are recombinant.

Lee *et al.*, *J. Clin. Microbiol.* 22:641-644 (1985), teach the use of purified herpes simplex virus type 2-specific glycoprotein (gG-2) in an immunodot enzymatic assay for the detection of HSV-2 antibodies in human serum. The gG-2 antigen used by Lee *et al.* (1985) was

purified from HSV-2-infected HEp-2 cells using immunoaffinity chromatography columns containing the anti-gG-2 mouse monoclonal antibodies H966 and H1206. Applicants respectfully submit that Lee *et al.* (1985) fail to disclose a **recombinant** gG-2 antigen.

Lee *et al.*, *J. Virol. Methods* 14:111-118 (1986), teach the purification of herpes simplex virus type 1-specific glycoprotein (gG-1) using the mouse monoclonal antibody H1379-2. Applicants respectfully submit that Lee *et al.* (1986) fail to disclose a **recombinant** gG-1 antigen.

Applicants respectfully submit that **recombinant** gG-1 and gG-2 glycoprotein antigens are structurally different from gG-1 and gG-2 glycoprotein antigens produced by herpes simplex virus types 1 and 2. As explained in the present specification, although the recombinant and gG-1 and gG-2 glycoproteins produced by the method described in the present application react with the same antibodies that react with non-recombinant HSV gG-1 and gG-2 glycoproteins, the recombinant proteins are different in that they are differently glycosylated than the non-recombinantly produced glycoproteins. (See page 25, line 20 to page 26, line 7 of the present specification.) Therefore, by describing the gG-1 and gG-2 antigens as "recombinant" antigens, they are by definition structurally different from the naturally-produced glycoproteins described by Lee *et al.* (1985) and Lee *et al.* (1986).

In the Advisory Action mailed April 24, 1997, the Examiner indicated that entry of the proposed amendment mailed March 14, 1997 would overcome the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §103 based on the article by Lee, Francis K., *et al.*, *J. Clin. Microbiol.* 22(4):641-644 (October 1985) and the article by Lee, Francis K., *et al.*, *J. Virol. Methods* 14:111-118 (1986). In view of the fact that both the non-entered amendment mailed March 14, 1997 and the amendment set forth above amend the claims to recite "recombinant" antigens, applicants respectfully request that the rejection be withdrawn.

The Examiner indicated in the Advisory Action mailed April 24, 1997, that he would maintain the rejection of Claims 7, 8, and 16 under 35 U.S.C. §103 as obvious over the articles of Lee *et al.*, (1985) or Lee *et al.* (1986) in view of the article of Luckow, Verne A., *et al.*, "Trends in the Development of Baculovirus Expression Vectors," *Bio/Technology*, 6:47-55 (January 1988) or the article of Matsuura, Yoshiharu, *et al.*, "Baculovirus Expression Vectors: the Requirements for High Level Expression of Proteins, Including Glycoproteins," *J. Gen. Virol.*, 68:1233-1250 (1987). The Examiner stated that the pending claims were product-by-process claims and implied that it would have been obvious to one skilled in the art to use the transfer

vectors as taught by Matsuura *et al.* and Luckow et al. to produce the claimed recombinant gG-1 and gG-2 antigens.

Applicants respectfully submit that one skilled in the art would not be motivated to modify the baculovirus expression vectors taught by Luckow *et al.* or the polyhedrin gene promoter taught by Matsuura *et al.* to produce the herpes simplex virus gG-1 and gG-2 antigens as claimed in Claims 7 and 8. Furthermore, there is no teaching in any of the references cited by the Examiner to combine the recombinant gG-1 or gG-2 antigens with a pharmaceutically acceptable carrier as claimed in Claim 16.

Lee *et al.* (1985) and (1986) teach the use of affinity chromatography-purified HSV gG-1 and gG-2 glycoproteins as described above.

Matsuura *et al.* teach that the polyhedrin gene promoter of *Autographa californica* nuclear polyhedrosis virus (AcNPV) is useful for high level expression of a glycoprotein of lymphocytic choriomeningitis virus. Matsuura *et al.* suggest that the synthesis is related to the integrity of the 5' non-coding region of the polyhedrin gene.

Luckow *et al.* is a review article directed to baculovirus expression vectors. Luckow *et al.* describe numerous factors affecting the expression of foreign genes by baculovirus vectors including optimizing placement of the foreign gene within the transfer vector.

Applicants respectfully submit that Luckow *et al.* and Matsuura *et al.* **fail** to teach, suggest or imply joining a foreign gene to the 5' nontranslated leader sequence of a polyhedrin gene **precisely** at the 5' translation initiation codon of the polyhedrin gene, **without either missing any nucleotide present in said initiation codon or introducing any extraneous nucleotide at the initiation codon site** as claimed in Claims 7 and 8 of the present application.

The Examiner further stated in the Advisory Action dated April 24, 1997, that applicants bear the burden of demonstrating distinctions between the claimed gG-1 and gG-2 antigens and gG-1 and gG-2 antigens produced by known methods. The Examiner has provided **no** evidence for the production of **recombinant** gG-1 and gG-2 antigens by methods other than those taught by applicants. Applicants respectfully submit that the claimed gG-1 and gG-2 antigens are structurally different from gG-1 and gG-2 antigens produced by known non-recombinant methods. Structural differences between the claimed recombinant HSV glycoproteins gG-1 and gG-2 and naturally produced gG-1 and gG-2 are shown in Figures 3 and 4 of the

scientific article by Sanchez-Martinez and Pellett, "Expression of HSV-1 and HSV-2 Glycoprotein G in Insect Cells by Using a Novel Baculovirus Expression Vector", *Virol.* 182:229-238 (1991). This article describes experimental data generated by the applicants that was included in Figures 3 and 4 and on page 21, lines 3-16 and page 23, lines 19-30 of the present specification. For example, Figure 3C of the Sanchez-Martinez and Pellett article provides an immunoblot analysis comparing the molecular weights of proteins extracted from Sf9 cells infected with the baculovirus vector AcDSMgG-1 containing the gG-1 gene (recombinant gG-1) with proteins extracted from HEp-2 cells infected with HSV-1 (non-recombinant gG-1). The recombinant gG-1 shows strong bands at 42 and 43 kDa, whereas the non-recombinant gG-1 shows a smear between 50 and 57 kDa. Similarly, Figure 4D of the Sanchez-Martinez and Pellett article provides an immunoblot analysis comparing the molecular weights of proteins extracted from Sf9 cells infected with the baculovirus vector AcDSMgG-2 containing the gG-2 gene (recombinant gG-2) with proteins extracted from HEp-2 cells infected with HSV-2 (non-recombinant gG-2). The recombinant gG-2 shows distinct bands at 107, 118, 128 and 143 kDa, whereas the non-recombinant gG-2 shows a smear between 78 and 118 kDa. It is well understood by those skilled in the art that proteins having different immunoblot band patterns are considered structurally different.

As discussed above, the claims of the present application are directed to **recombinant** HSV gG-1 and gG-2 antigens produced from a novel baculovirus vector. Not only are the recombinant antigens structurally different from **naturally** produced gG-1 and gG-2 antigens as described above, but the claimed recombinant antigens are produced in greater quantities thereby yielding a purer product than recombinant gG-1 and gG-2 antigens produced using vectors such as vaccinia vectors or alternative baculovirus systems such as the pAc373 baculovirus system. In addition, the claimed recombinant gG-1 and gG-2 proteins are produced in the absence of the other 80 herpes simplex virus proteins that are produced naturally by herpes simplex virus type 1 or herpes simplex virus type 2-infected mammalian cells. Nearly every gene encoded by herpes simplex virus type 1 has a genetic counterpart in herpes simplex virus type 2, and the protein products of these homologous genes have significant antigenic cross-reactivity, except for gG-1 and gG-2. This is the basis of the unique utility of these proteins for construction of HSV type-specific serologic assays. The claimed proteins are therefore much purer and less likely to be contaminated by HSV-type cross-reactive antigens than gG-1 and gG-2 proteins produced by known methods.

Conclusion

In conclusion, applicants respectfully submit that Claims 7, 8 and 16 are novel and non-obvious in view of the references cited by the Examiner.

Applicant maintains that the claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited. If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 818-3773 is courteously solicited.

Respectfully submitted,
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Attorney Docket No. 03063-0111
May 14, 1997